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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/531,088	03/18/2000	Christopher J. Horvath	10147-22 (MPI2000-131)	5277

570 7590 10/18/2002

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EXAMINER	
ROARK, JESSICA H	

ART UNIT	PAPER NUMBER
1644	15

DATE MAILED: 10/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/531,088	Applicant(s) HORVATH, CHRISTOPHER J.
	Examiner Jessica H. Roark	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33,47 and 48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33,47 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 July 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 7/28/02(Paper No. 13), is acknowledged.
Claims 34-46 have been cancelled.
Claims 2-3, 9, 12 and 22 have been amended.
Claims 1-33 and 47-48 *are pending and are under consideration in the instant application.*

2. Applicant's Second Petition under 37 CFR 1.10(d), filed 4/15/02, is acknowledged. However, as set forth in Paper No. 11 (7/8/02) this Petition has been dismissed.

The filing date of the instant application is therefore considered to be 3/18/2000.

3. Applicant's provision of new copies of certain of the references cited on the IDSs, filed 1/19/01 and 6/29/01, is gratefully acknowledged.

These references have now been considered, as indicated on the attached copy of the 1449.

4. This Office Action will be in response to applicant's arguments, filed 7/28/02 (Paper No. 13). The rejections of record can be found in the previous Office Action (Paper No. 9).

It is noted that New Grounds of Rejection are set forth herein.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112.

> *The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

6. Claims 3-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3-4 are indefinite in the recitation of monoclonal antibody "1B4" because its characteristics are not known. The use of "1B4" as the sole means of identifying the claimed antibody renders the claim indefinite because "1B4" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designations to define completely distinct antibodies/hybridomas.

Applicant's arguments, filed 7/26/02 have been fully considered but have not been found persuasive. Applicant argues that the 1B4 antibody was deposited by others in U.S. Pat. No. 5,147,637 (of record) and is the same as the antibody produced by the cell line ATCC # HB-10164.

However, the instant claims do not recite ATCC Deposit # HB-10164. In addition, it is noted that the antibody referred to in U.S. Pat. No. 5,147,637 (of record) and in the ATCC Deposit information for HB-10164 (ATCC Cell Lines and Hybridomas, 8th Edition 1994 pages 491-492) is to the IB4 antibody, not the "1"B4 antibody.

Applicant should amend the claims to recite ATCC Deposit # HB-10164 in order to obviate this rejection.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

7. Applicant's amendment, filed 7/26/02 has obviated the previous rejection of claims 2-3 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention with respect to the terms "substantially only" and "similar to".

8. The previous rejection of claims 3-4 under 35 U.S.C. 112, first paragraph, (deposit enablement) is withdrawn in view of the support on page 49, Table C, that the antibody in question is the same as that of ATCC Deposit No. HB-10164, pointed to by Applicant in the response filed 7/26/02.

It is further noted that the deposit of the HB-10164 cell line was made under terms of the Budapest Treaty and that all restrictions upon its availability were irrevocably removed upon granting of U.S. Pat. No. 5,147,637.

Therefore, the deposit requirement with respect to the HB-10164 cell line is considered to be fulfilled.

9. Applicant's amendment, filed 7/26/02, has obviated the previous rejection of claim 3 under 35 U.S.C. 112, first paragraph, with respect to lack of enablement of an antibody which has an epitopic specificity that is "similar to" that of monoclonal antibody 1B4.

10. Applicant's arguments, filed 7/26/02, have been found convincing with respect to the previous rejection of claims 1-33 and 47-48 under 35 U.S.C. 112, scope of enablement and written description. The previous rejection of claims 1-33 and 47-48 under 35 U.S.C. 112, scope of enablement and written description is withdrawn.

11. Applicant's arguments, filed 7/26/02, have been found convincing with respect to the previous rejection of claims 1-3, 5-20, 24, 26-33 and 47-48 under 35 U.S.C. 102(b) as being anticipated by Waldmann et al. (U.S. Pat. No. 5,997,867, of record), as evidenced by Rogers et al. (WO 98/42360, IDS). The previous rejection of claims 1-3, 5-20, 24, 26-33 and 47-48 under 35 U.S.C. 102(b) as being anticipated by Waldmann et al. (U.S. Pat. No. 5,997,867, of record), as evidenced by Rogers et al. (WO 98/42360, IDS) is withdrawn.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-3, 5-33 and 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rogers et al. (WO 98/42360, IDS) in view of Waldmann et al. (U.S. Pat. No. 5,997,867, of record).

Applicant's arguments, filed 7/26/02, have been fully considered but have not been found persuasive, essentially for the reasons of record in Paper No. 9.

Applicant's arguments are addressed following a re-iteration of the rejection as applied to the instant claims.

As previously noted, Rogers et al. teach that administering antibodies to Mac-1, which is a leukocyte cell surface protein that comprises CD18, reduces neointimal thickening after balloon and stent-induced vascular injury in an animal model of restenosis. Roger et al. further teach that antibodies to Mac-1 can be used in humans to lessen restenosis of blood vessels after revascularization, via angioplasty or bypass surgery, of diseased coronary and cerebral arteries, and lessen stenosis and restenosis of surgically –placed bypass grafts (see entire document, e.g., "Abstract").

Rogers et al. review the art-recognized role of MAC-1 in neutrophil accumulation and migration at sites of vascular injury (e.g., pages 8-9). Rogers et al. further teach that antibody administration blocks binding of Mac-1 (CD11b/CD18) to multiple ligands (e.g., page 9 at line 9-24) and that these ligands include ICAM-1, factor X and fibrin and fibrinogen (page 8 at lines 21-27 and pages 23-24). That various proteins comprised of CD18 are expressed on leukocytes, including neutrophils, is also taught (e.g., page 9, especially lines 9-24). Rogers et al. also teach that functions associated with the binding of a natural ligand to a protein comprising CD18 include binding, translocation and infiltration of leukocytes through the vascular endothelium into intimal vascular tissue (see entire document, especially pages 1-9).

Rogers et al. teach that the administered antibodies may be humanized or used as fragments that are well known in the art (see page 10, especially lines 1-6). Administration of antibody to blood vessels prior to, at the time of, or following injury is taught (e.g., pages 19- 20, especially page 20 at lines 1-6)

Rogers et al. do not teach administering antibodies which bind specifically with only the CD18 portion of a protein comprising CD18.

Although Rogers et al. exemplify an anti-Mac-1 antibody that does not bind only to the CD18 portion of Mac-1 (e.g., page 9), Rogers et al. also clearly recognize that other monoclonal antibodies can be substituted for use in these methods (e.g., page 9, especially in view of the fact that the CD18 portion is the common component shared by the integrins Mac-1, LFA-1 p150,95 and CD11d/CD18, taught as targets on page 8 and pages 23-24).

Waldmann et al. have been discussed previously and in brief teach a method for treating a patient suffering from a leukocyte-mediated reperfusion damage by administering a humanized antibody to CD18 (see entire document, especially claims 1-9). Waldmann et al. further teach that the substitution of a humanized antibody for rat or mouse antibody avoids the unwanted anti-mouse/rat immune response that is elicited when a rat or mouse antibody is administered to a human (e.g., see column 1, especially lines 37-49). Waldmann et al. also teach and claim the treatment of reperfusion damage post thrombolytic therapy (e.g., claim 6).

Waldmann et al., like Rogers et al., also teach that the humanized anti-CD18 antibody may be provided to the blood vessel (i.e., "intravenously", e.g., column 8 especially lines 63-67) either prior to (e.g., column 9 especially lines 63-67) or after (e.g., column 9, especially lines 41-47) development of the reperfusion damage.

Because the antibody of Waldmann et al. binds CD18, it would be a competitive inhibitor of binding of the 1B4 antibody to human CD18.

Given the teachings of the references, it would have been obvious to the ordinary artisan at the time the invention was made to substitute or combine the humanized anti-CD18 antibody taught by Waldmann et al. for the anti-Mac-1 antibody taught by Rogers et al.

The ordinary artisan would have been motivated to make such a substitution with the expectation that a humanized anti-CD18 antibody would function even better than the antibody of Rogers et al. which recognized the Mac-1 antigen comprising CD18 (CD11b/CD18). The ordinary artisan would have been further motivated to make the substitution because the humanized antibody, unlike the antibody of Rogers et al., would not have been expected to elicit an unwanted immune response to the antibody itself when administered to a human. In addition, the ordinary artisan would have been motivated to substitute an anti-CD18 antibody for an antibody recognizing only Mac-1 because blocking the common CD18 component of 4 integrins, all of which were known at the time the invention was made to be involved in leukocyte recruitment, would be expected to be more beneficial than blocking a single CD18-containing integrin.

Given that the humanized anti-CD18 antibody of US 5,997,867 was also known to be therapeutic in treating patients suffering in general from leukocyte-mediated disease, including leukocyte-mediated reperfusion damage in general and leukocyte-mediated reperfusion damage due to post thrombolytic therapy; the ordinary artisan would have had a reasonable expectation of successfully substituting or combining the anti-CD18 antibody for the anti-Mac-1 antibody. The various forms of antibody administered (fragments, chimeric, human) appear to represent variations that were well known in the art at the time the invention was made. In addition, given the teachings that administration of anti-CD18 antibodies could be used to inhibit restenosis after interventional therapies such as angioplasty, it would also have been obvious to the ordinary artisan at the time the invention was made to utilize the antibody therapy in the related condition wherein the blood vessel has non-traumatically deteriorated, including for atherosclerosis.

Applicant argues that there was no motivation to combine the teachings of Rogers et al. and Waldmann et al., and points to the teachings of Guzman et al. (Coronary Artery Disease 1995; 6:693-701, IDS) for support that the artisan at the time the invention was made would not have been motivated to substitute an anti-CD18 antibody for the anti-Mac-1 antibody of Rogers et al. because Guzman et al. teach that anti-CD18 antibody therapy did not inhibit restenosis following balloon angioplasty.

While the Examiner acknowledges the teachings of Guzman et al.; it is noted that the teachings of Rogers et al. post-date the teachings of Guzman et al. by several years. In addition, there are significant differences between the methodology employed by Guzman et al. versus that of Rogers et al. Guzman et al. administered the anti-CD18 antibody at only two time points - 12 hours before balloon angioplasty and again 48 hours later (see "Antibody Administration" page 695). In contrast, Rogers et al. administered the anti-Mac-1 antibody 2hrs before balloon angioplasty and every other day for two weeks (see "Example 2, pages 21-22). Thus the ordinary artisan would have recognized that the results obtained by Guzman et al. in view of the results obtained by Rogers et al. only taught the importance of continued antibody administration to suppress restenosis following angioplasty.

Applicant also argues that Rogers et al. do not teach or suggest that an antibody to CD18 could be used to inhibit vascular stenosis/restenosis.

However, as noted supra, Rogers et al. do teach that CD18 is the common component shared by the integrins Mac-1, LFA-1 p150,95 and CD11d/CD18 each of which are involved in leukocyte adhesion and taught as targets on page 8 and pages 23-24. Thus given the teachings of Rogers et al. that an antibody that inhibits leukocyte adhesion via one of these molecules, Mac-1, could be used to inhibit or reduce stenosis or restenosis; the ordinary artisan would have found it obvious to use antibodies to any of these integrins, but would have been particularly motivated to select an anti-CD18 antibody because CD18 is a component of not only Mac-1, but also LFA-1, p150,95 and CD11d/CD18.

Applicant further argues that the teachings of Waldmann et al. relate to inhibition of reperfusion injury, not stenosis/restenosis; and that therefore the ordinary artisan would not have been motivated to utilize the anti-CD18 antibody of Waldmann et al. in the methods of Rogers et al.

For the reasons set forth supra the ordinary artisan would have been motivated to substitute or combine an anti-CD18 antibody for theanti-Mac-1 antibody of Rogers et al. even without the teachings of Waldmann et al. However, Waldmann et al. teach a humanized anti-CD18 antibody, and discuss the reasons why an ordinary artisan would have been motivated to select a humanized antibody for use in human therapies. In addition, while the Examiner acknowledges that stenosis/restenosis are not reperfusion injuries, stenosis/restenosis was well known to be a chronic complication to arise following reperfusion injuries, particularly those due to thrombolytic therapies, as taught by Waldmann et al. In addition, Waldmann et al., like Rogers et al., teach that it is the inhibition of leukocytes that leads to the inhibition of both reperfusion injury due to thrombolytic therapies (Waldmann et al.) and stenosis/restenosis (Rogers et al.)

Thus the Examiner maintains that the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rogers et al. (WO 98/42360, IDS) in view of Waldmann et al. (U.S. Pat. No. 5,997,867, of record) as applied to claims 1-3, 5-33 and 47-48 above, and further in view of Wright et al. (U.S. Pat. No. 5,147,637, IDS).

Applicant's arguments, filed 7/26/02, have been fully considered but have not been found convincing, essentially for the reasons of record in Paper No. 9, and as elaborated upon supra.

Applicant argues that the rejection of claim 4 should be withdrawn for the reasons set forth with respect to the rejection of claims 1-3, 5-33 and 47-48 as being unpatentable over Rogers et al. (WO 98/42360, IDS) in view of Waldmann et al. (U.S. Pat. No. 5,997,867, of record).

The Examiner has not found these arguments convincing, as detailed supra.

The rejection of record is re-iterated below:

The claims are drawn to a method of inhibiting stenosis in a blood vessel comprising administering the 1B4 antibody.

Rogers et al. (WO 98/42360, IDS) in view of Waldmann et al. (U.S. Pat. No. 5,997,867, of record) as applied to claims 1-3, 5-33 and 47-48 has been discussed supra.

Rogers et al. (WO 98/42360, IDS) in view of Waldmann et al. (U.S. Pat. No. 5,997,867, of record) do not teach the 1B4 anti-CD18 antibody.

Wright et al. teach the 1B4 antibody deposited with the ATCC as HB 10164, and that the 1B4 antibody to CD18 can be used to inhibit the binding of leukocytes to endothelium and their influx into tissues (see entire document).

For the reasons set forth supra one of ordinary skill in the art at the time the invention was made would have recognized that any of a number of antibodies could be substituted into the instant method. Given the teachings of the particular 1B4 antibody and that it binds to CD18 and inhibits leukocyte influx into organs, the ordinary artisan would have had a reasonable expectation that the 1B4 antibody could also be substituted into the methods taught by Rogers et al. in view of Waldmann et al. with a reasonable expectation that the 1B4 antibody would function as expected based upon its specificity and known activity. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. No claim is allowed.

16. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica H. Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday, 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
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October 17, 2002

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